Disease Burden, Patient Experiences, & Unmet Needs in Refractory Rheumatoid Arthritis: Insights from 20 Years of Real-World Data

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Individuals with refractory RA have significantly higher healthcare utilization, glucocorticoid use, and greater odds of GI disorder compared to individuals with exposure to only one advanced therapy.

FORWARD
The National Databank for Rheumatic Diseases

BACKGROUND

- Despite major advances in RA treatment, a substantial number of patients (~6-21%, depending on the definition used[1]) are refractory to multiple advanced therapies
- Refractory RA (reRA) is a subset of the heterogeneous difficult to treat RA (D2T RA)
- The lack of a standardized reRA definition leads to inconsistency and hinders research
- Real-world data and patient-reported outcomes (PROs) are essential for personalized approaches and to understand patient experiences and unmet needs, but are underutilized in reRA definitions[2]
- Objective: to identify factors associated with reRA and characterize differences in burden/patient experiences between reRA and matched nonrefractory controls, from 20 years of real-world data

METHODS

- Data were provided by adults with RA in the FORWARD Databank from 1998 to 2019
- Participants with no history of biologic (bDMARD) or targeted synthetic DMARD (tsDMARD) use at study entry but with subsequent exposure to one or more advanced therapies were included
- reRA: exposure to ≥3 advanced therapies during observation, with ≥1 TNFi and at ≥1 tsDMARD or non-TNFi bDMARD
- Nonrefractory: continued use of first advanced therapy for ≥2 years and never exceeded two advanced therapy exposures
- Participants were matched 1:1 on age, sex, RA duration, calendar year, and observation time
- Descriptive statistics were calculated at initiation of first advanced therapy and at the point of meeting reRA criteria (matched time point for nonrefractory controls)
- Consequential covariates were identified with LASSO and included in multivariable logistic regression models for each time point

RESULTS

Table 1. Characteristics of FORWARD participants with RA at baseline (initiation of first advanced therapy) and follow up (the point of meeting reRA criteria; matched time point for nonrefractory controls) by reRA status. n=692 for each group. Significance was assessed with Chi-square and t-tests, as appropriate. Significant differences are shown in bold. Healthcare interactions were in the six-month period prior to the observation.

	Baseline		Follow Up	
	Nonrefractory	Refractory	Nonrefractory	Refractory
Demographics				
Age, years	56.7 (11.4)	56.4 (10.9)	62.7 (12.0)	62.3 (11.5)
Female, %	88.2	88.2	88.2	88.2
White, %	92.0	91.2	92.0	91.2
Education, years	13.9 (2.4)	14.1 (2.2)	13.9 (2.4)	14.1 (2.2)
Rural residence, %	23.1	26.6	23.1	26.6
Hx smoking, %	49.7	50.3	51.9	53.3
BMI	28.0 (7.2)	28.4 (6.4)	28.1 (7.4)	28.8 (6.7)
Duration, years	14.5 (10.3)	14.4 (10.7)	20.5 (11.3)	20.4 (11.6)
Concomitant Medications				
Glucocorticoid, %	**40.1**	**46.1**	**33.0**	**47.0**
csDMARD, %	84.6	85.7	70.8	71.8
NSAID, %	64.8	61.6	43.3	43.8
Weak opioid, %	**22.0**	**28.2**	**25.8**	**32.2**
Strong opioid, %	3.8	5.6	**5.9**	**9.4**
Patient-Reported Outcomes				
Pain VAS, 0-10	**3.5 (2.7)**	**4.3 (2.8)**	**3.7 (2.8)**	**4.5 (2.6)**
Fatigue VAS, 0-10	**4.2 (2.9)**	**4.8 (3.0)**	**4.5 (3.1)**	**5.1 (2.9)**
Patient Global VAS, 0-10	**3.4 (2.5)**	**4.0 (2.5)**	**3.7 (2.5)**	**4.4 (2.3)**
HAQ-II, 0-3	**1.0 (0.7)**	**1.1 (0.7)**	**1.0 (0.8)**	**1.2 (0.7)**
PAS-II, 0-10	**3.4 (2.2)**	**4.0 (2.1)**	**3.6 (2.3)**	**4.3 (2.0)**
Comorbidities				
RDCI, 0-9	**1.4 (1.4)**	**1.7 (1.5)**	**1.9 (1.6)**	**2.1 (1.7)**
Pulmonary disorder, %	28.3	26.4	43.2	45.1
Cardiac disorder, %	17.3	19.4	32.2	32.7
Hx fracture, %	16.2	16.8	**27.5**	**31.6**
Hx depression, %	38.8	41.1	52.2	55.1
Diabetes, %	9.5	10.4	18.7	18.4
Hx cancer, %	16.2	14.5	29.9	25.1
GI disorder, %	**50.5**	**57.9**	**66.8**	**74.4**
PSD, 0-31	**10.3 (7.2)**	**11.8 (7.5)**	**10.7 (7.7)**	**12.6 (7.7)**
Fibromyalgia criteria, %	**22.5**	**28.2**	**23.2**	**32.9**
Healthcare Interactions				
Rheumatology visits	3.4 (1.9)	3.6 (2.0)	**2.5 (1.7)**	**3.4 (2.0)**
Family medicine visits	2.3 (1.9)	2.3 (1.7)	2.2 (1.8)	2.3 (1.8)
Gastroenterology visits	0.8 (1.3)	0.8 (1.0)	0.6 (1.1)	0.7 (1.0)
Other specialist visits	2.1 (2.3)	2.0 (2.2)	2.2 (2.2)	2.1 (2.1)
ER visits	0.7 (0.8)	0.7 (0.9)	0.6 (0.7)	0.7 (0.8)
Any hospitalization, %	10.0	11.3	10.0	13.3
Hospitalized for infection, %	2.7	1.7	2.5	3.3
Health satisfaction, 0-4	**2.4 (1.2)**	**2.0 (1.3)**	**2.3 (1.2)**	**1.9 (1.2)**

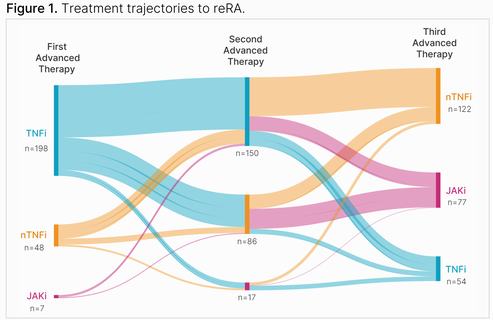
csDMARD=conventional synthetic DMARD; weak opioid=codeine, tramadol, hydrocodone; strong opioid=morphine, fentanyl, methadone, hydromorphone, oxycodone, oxymorphone; VAS=visual analog scale; PAS-II=Patient Activity Scale II; RDCI=Rheumatic Disease Comorbidity Index; PSD=polysymptomatic distress.

- Of 6,575 who met inclusion criteria, 718 (10.9%) met reRA criteria
- Of those, 692 were matched 1:1 to nonrefractory controls, for a total of 1,384 participants included in the study
- Significant baseline predictors of reRA included education (1.1 [1.0, 1.1], p=0.02) and health satisfaction (0.8 [0.7, 0.9], p=0.002)
- Factors significantly associated with reRA included number of rheumatology visits in the previous six months (>4 visits 3.8 [2.7, 5.4], p<0.001; 3-4 visits 1.9 [1.5, 2.5], p<0.001), glucocorticoid use (1.5 [1.2, 2.0, p<0.001], GI disorder (1.5 [1.1, 1.9], p=0.005), education (1.1 [1.0, 1.1], p=0.008), and history of cancer (0.7 [0.6, 1.0], p=0.03).

Table 2. Initial advanced therapy by refractory status. Values are n(%).

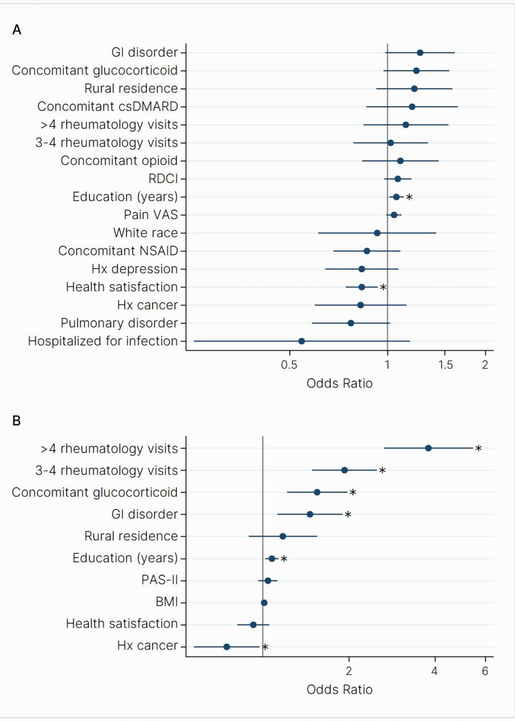
Medication (category)	Non-refractory controls	Refractory
Etanercept (TNFi)	265 (38.3)	297 (42.9)
Infliximab (TNFi)	237 (34.3)	192 (27.8)
Adalimumab (TNFi)	113 (16.3)	97 (14.0)
Abatacept (nTNFi)	30 (4.3)	33 (4.8)
Rituximab (nTNFi)	16 (2.3)	8 (1.2)
Tofacitinib (JAKi)	9 (1.3)	7 (1.0)
Tocilizumab (nTNFi)	7 (1.0)	10 (1.5)
Golimumab (TNFi)	7 (1.0)	8 (1.2)
Certolizumab (TNFi)	6 (0.9)	15 (2.2)
Anakinra (nTNFi)	2 (0.3)	25 (3.6)

Figure 1. Treatment trajectories to reRA.



TNFi=tumor necrosis factor inhibitor; nTNFi=non-TNFi biologic DMARD; JAKi=Janus kinase inhibitor

Figure 2. Multivariable logistic regression results for **(A)** baseline predictors of reRA and **(B)** factors associated with reRA at the time of meeting reRA criteria. Characteristics from Table 1 identified as consequential with LASSO were included in each model. Statistically significant (p<0.05) covariates are labeled with an asterisk (*). Rheumatology visits (0-2 visit reference) and hospitalization were within the six-month period prior to the observation.



GI=gastrointestinal; csDMARD=conventional synthetic DMARD; RDCI=Rheumatic Disease Comorbidity Index. VAS=visual analog scale. PAS-II=Patient Activity Scale II.

CONCLUSION

- Exposure to numerous advanced RA therapies is associated with significant disease burden and unmet healthcare needs, as evidenced by lower health satisfaction, higher rates of glucocorticoid use, greater comorbidity burden, and more rheumatology visits
- These results provide important information about PROs and patient experiences that can guide ongoing efforts to differentiate reRA from the broader D2T RA
- These findings underscore the importance of well-defined reRA criteria and the need for further investigation into this RA phenotype to identify targeted treatment strategies and ultimately improve outcomes

DISCLOSURES

- This study was funded by Janssen Pharmaceuticals.

REFERENCES

- 1 Melville, A. R. et al. Drugs 80, 849–857 (2020)
- 2 Chaplin, H. et al. Rheumatology 60, 3540-3552 (2021)

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